

## **REMARKS**

### **Amendments to the Specification**

Applicants have amended paragraph 40 of the specification to remove an embedded hyperlink, as requested by the Examiner. Accordingly, reconsideration and withdrawal of this objection to the disclosure is respectfully requested.

### **Amendments to the Claims**

By this Amendment, Applicants have cancelled claims 4, 6, 26, 28, and 36, and amended claims 1, 2, 5, 7-11, 16, 17, 29-33, and 38. In addition, Applicants have added new claim 39, directed to humanized or human antibodies. Claims 1, 2, 16, 17, and 38 have been amended to change "TGF- $\beta$  antagonist" to "anti-TGF- $\beta$  antibody" and "RAAS antagonist" to "ACE inhibitor". Support for these amendments can be found throughout the application and original claims, for example in original claims 4, 6, 26, and 28. Claims 10 and 32 have been amended to recite an "antibody comprising CDR sequences identical to 1D11, wherein 1D11 is the antibody deposited with the American Type Culture Collection (ATCC) under Designation No. HB 9849." Support for these amendments and new claim 39 can be found, for example, at paragraphs 15 and 47 of the specification. Claims 5, 7-9, 11, 29-33 have been amended to correct their dependencies from cancelled claims 4, 6, and 28.

### **Double patenting**

The Examiner has objected to claim 36 as a substantial duplicate of claim 22. Applicants have cancelled claim 36, thus rendering this objection moot, and acknowledgement of such is respectfully requested.

## Claim Rejections

### A. 35 U.S.C. § 112

The Examiner has rejected claims 1-5, 13, 16-19, 22-26, and 35-38 under 35 U.S.C. § 112, first paragraph as allegedly lacking enablement for all possible TGF- $\beta$  antagonists and RAAS antagonists. (Office Action at p. 4.)

While Applicants disagree with the Examiner regarding enablement of the pending claims, for the purposes of advancing prosecution, Applicants have amended the claims to recite an "anti-TGF- $\beta$  antibody" and an "ACE inhibitor". Both of these groups of antagonists are fully enabled, as Applicants have provided detailed definitions of TGF- $\beta$  antibodies and ACE inhibitors (see, e.g., paragraphs 27 and 33 of the specification), and disclosed multiple working examples using anti-TGF- $\beta$  antibodies and ACE inhibitors (e.g., both lisinopril and enalapril, see Examples 1-9.) In addition, the Examiner has acknowledged that the specification is enabling for a method of treatment wherein the TGF- $\beta$  antagonist is an anti-TGF- $\beta$  antibody. (Office Action at p. 3.)

Therefore, Applicants respectfully submit that the claim amendments obviate the rejection, and reconsideration and withdrawal of the rejection are respectfully requested.

The Examiner has also rejected claims 10 and 32 under 35 U.S.C. § 112, second paragraph, as being indefinite. In particular, the Examiner objects to the term "derivative", and states that it is unclear "what additional or material limitations are placed upon a claim by the presence of this element." (Office Action at p. 6.)

While Applicants respectfully disagree that the cited language is indefinite, claims 10 and 32 have been amended to recite an "antibody comprising CDR sequences

identical to those of 1D11, wherein 1D11 is the antibody deposited with the American Type Culture Collection (ATCC) under Designation No. HB 9849." The term antibody has been defined at paragraph 27 of the specification, and support for the CDR sequence limitations can be found, for example, at paragraph 47 while support for the ATCC Designation No. can be found, for example, at paragraph 15. In addition, one of skill in the art would recognize CDR sequences as structural features important for antibody specificity.

Therefore, Applicants submit that the amended claims are not indefinite, and respectfully request reconsideration and withdrawal of this rejection.

B. 35 U.S.C. § 103

The Examiner has rejected claims 1-4, 6, 13-19, 22-26, 28, and 35-38 under 35 U.S.C. § 103(a) as allegedly being unpatentable over *Border* and *Reeves*. (Office Action at p. 7.) Specifically, the Examiner asserts that "it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to treat a mammal having a renal disorder or diminished renal function by administering to the mammal a therapeutically effective amount of a TGF $\beta$  antagonist and a therapeutically effective amount of a RAAS antagonist." (Office Action at p. 9.) Applicants respectfully traverse this rejection in view of the claim amendments presented above and for the reasons explained further below.

As an initial matter, Applicants note that the claims have been amended to specify that the TGF- $\beta$  antagonist employed in the claimed method is an anti-TGF- $\beta$  antibody, and the RAAS antagonist employed in the claimed method is an ACE inhibitor. Accordingly, the generalized teachings in *Border* and *Reeves* that it might be

desirable to target the TGF- $\beta$  pathway and/or the RAAS pathway do not immediately suggest the claimed method (i.e., limited to a method employing an anti-TGF- $\beta$  antibody and an ACE inhibitor). Indeed, the promise that "[h]igher doses or different combinations of drugs that block the renin-angiotensin system or entirely new drug strategies may be needed to achieve a greater antifibrotic effect" (*Border* at p. 181, Abstract; and Office Action at p. 7-8) neither suggests the specific method claimed, nor provides a reasonable expectation of achieving the treatment efficacy shown by Applicants for the instantly claimed method. In fact, *Reeves* describes numerous proteins involved in the TGF- $\beta$  pathway, further decreasing the certainty that any particular combination of therapeutic approaches would be significantly more successful than individual therapies known at the time.

According to *Border*, TGF- $\beta$  mediates "a good deal of renal and cardiac fibrosis associated with activation of the RAS" (p. 181, right column), and RAS and TGF- $\beta$  pathways have significant interplay between their feedback mechanisms. Furthermore, *Reeves* teaches "it is quite likely that some of the beneficial effects of ACE-I in diabetic nephropathy (and other kidney diseases) are related to suppression of TGF- $\beta$  production." (*Reeves*, p. 7668, right column.) *Reeves* further cites *Border*, and provides attempts to describe the complexity of TGF- $\beta$ 's role in diabetic nephropathy. While *Reeves* provides generalized teachings similar to those of *Border*, neither suggests to one skilled in the art that the level of beneficial effects achieved by Applicants using the instantly claimed method could be achieved. Indeed, the combined teachings of *Border* and *Reeves* would lead the skilled artisan to expect that a dual therapy targeting both the RAS pathway and the TGF- $\beta$  pathway would result in

only a minor, if any, improvement in therapeutic effect over each individual treatment. This is because of the “biologically rich and complex interaction between the RAS and TGF- $\beta$  in which both act at various points to regulate the actions of the other” (Border at 181, left column), and the fact that each treatment affects the same renal pathological process. Further, *Border* discloses that administration of an ACE inhibitor actually *increased* expression of renin and TGF- $\beta$ . (*Border* at p. 182, right column.) Accordingly, *Border* teaches away from the claimed method because it suggests that administration of an ACE inhibitor with a TGF- $\beta$  antagonist could actually interfere with the TGF- $\beta$  lowering effects of the TGF- $\beta$  antagonist treatment.

Following the teachings of *Border* and *Reeves*, one of skill in the art would not expect co-administration of an anti-TGF- $\beta$  antibody with an ACE inhibitor to achieve the surprising efficacy in improvement of therapeutic endpoints that Applicants have demonstrated. For instance, Example 9 (Tables 6 and 7 at p. 40) and Figure 4 demonstrate that the claimed combination therapy achieves therapeutic benefits much greater than each individual therapy, and, indeed, comparable in nature to that of the positive control animals.

Therefore, the combined generalized teachings of *Border* and *Reeves* neither suggest the instantly claimed combination therapy using an anti-TGF- $\beta$  antibody and an ACE inhibitor, nor do they provide a reasonable expectation of success in achieving the unexpected therapeutic benefits that Applicants have demonstrated using the instantly claimed method. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

The Examiner has also rejected claims 1-4, 6-8, 10, 13-19, 22-26, 28-30, 32, and 35-38 over *Border*, *Reeves*, and further in view of *Ledbetter*. In particular, the Examiner states that "it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to treat a mammal having diminished renal function...to modify that teaching (of *Border* and *Reeves*) by administering a human anti-TGF $\beta$  antibody, a humanized anti-TGF $\beta$  antibody, 1D11 or a humanized derivative of 1D11, as taught by *Ledbetter*, with a reasonable expectation of success." (Office Action at p. 13.) Applicants respectfully disagree.

*Ledbetter* discloses treatment of renal disorders using TGF- $\beta$  antagonists, including anti-TGF- $\beta$  antibodies, but does not disclose the use of ACE inhibitors. Accordingly, *Ledbetter* does not cure the defects of the combined teachings of *Border* and *Reeves* in suggesting the claimed combination therapy using an anti-TGF- $\beta$  antibody and an ACE inhibitor or in demonstrating that the claimed combination therapy would achieve the unexpectedly beneficial therapeutic effects shown by Applicants.

Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

Finally, the Examiner has rejected claims 1-8, 10, 13-19, 22-26, 28-30, 32, and 35-38 over *Border*, *Reeves*, *Ledbetter*, and further in view of *Agarwal*. In particular, the Examiner asserts that "it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to treat a mammal having diminished renal function....to modify that teaching (of *Border* and *Reeves* in view of *Ledbetter*) by administering a therapeutically effective amount of lisinopril, as taught by *Agarwal*, with

a reasonable expectation of success." (Office Action at p. 15.) Applicants respectfully disagree.

*Agarwal* teaches ACE inhibitor therapy for renoprotection, but does not teach the combination of TGF- $\beta$  antagonists with RAAS inhibitors in general, let alone the instantly claimed combination therapy using an anti-TGF- $\beta$  antibody and an ACE inhibitor. Further, *Agarwal* adds nothing to the combined teachings of *Border* and *Reeves* in demonstrating that the claimed combination therapy would achieve the unexpectedly beneficial therapeutic effects shown by Applicants. Accordingly, *Agarwal* does not cure the defects in the combined teachings of *Border* and *Reeves*, either with or without the further teachings of *Ledbetter*.

Therefore, reconsideration and withdrawal of the rejection is respectfully requested.

### **CONCLUSION**

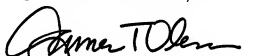
Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,  
GARRETT & DUNNER, L.L.P.

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By:

  
James T. Olesen  
Reg. No. 46,967  
617.452.1640